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Miyazakia, Yasushi ; Tauro, Sudhir

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Research paper

Differing clinical features between Japanese and Caucasian patients with myelodysplastic syndromes: Analysis from the International Working Group for Prognosis of MDS

Yasushi Miyazaki[a,*], Heinz Tuechler[b], Guillermo Sanz[c], Julie Schanz[d], Guillermo Garcia-Manero[e], Francesc Solé[f], John M. Bennett[g], David Bowen[h], Pierre Fenaux[i], Francois Dreyfus[j], Hagop Kantarjian[e], Andrea Kuendgen[k], Luca Malcovati[l], Mario Cazzola[l], Jaroslav Cermak[m], Christa Fonatsch[n], Michelle M. Le Beau[o], Marilyn L. Slovak[p], Valeria Santini[q], Michael Lübbert[r], Jaroslaw Maciejewski[s], Sigrid Machherndl-Spandl[t], Silvia M.M. Magalhaes[u], Michael Pfeilstöcker[v], Mikkael A. Sekeres[s], Wolfgang R. Sperr[w], Reinhard Stauder[x], Sudhir Tauro[y], Peter Valent[w], Teresa Vallespi[z], Arjan A. van de Loosdrecht[A], Ulrich Germing[k], Detlef Haase[d], Peter L. Greenberg[B]

[a] Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
[b] L. Boltzmann Institute for Leukemia Research, Vienna, Austria
[c] Hospital Universitario La Fe, Valencia, Spain
[d] University Medical Center, Clinics of Haematology and Medical Oncology, Göttingen, Germany
[e] The University of Texas MD Anderson Cancer Center, Houston, TX, United States
[f] Institut de Recerca contra la Leucèmia Josep Carreras, Barcelona, Spain
[g] James P. Wilmot Cancer Center, University of Rochester Medical Center, Rochester, NY, United States
[h] St James's University Hospital, Leeds, United Kingdom
[i] Hopital Avicenne, Assistance Publique–Hopitaux de Paris (AP-HP)/University of Paris XIII, Bobigny, France
[j] Hopital Cochin, AP-HP, University of Paris V, Paris, France
[k] Heinrich-Heine University Hospital, Dusseldorf, Germany
[l] Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Matteo and University of Pavia, Pavia, Italy
[m] Institute of Hematology and Blood Transfusion, Praha, Czech Republic
[n] Medical University of Vienna, Vienna, Austria
[o] University of Chicago Comprehensive Cancer Research Center, Chicago, IL, United States
[p] Department of Pathology, University of New Mexico, Albuquerque, NM, United States
[q] MDS Unit, Ematologia, AOU Careggi, Università degli Studi di Firenze, Firenze, Italy
[r] University of Freiburg Medical Center, Faculty of Medicine, Freiburg, Germany
[s] Cleveland Clinic, Cleveland, OH, United States
[t] Elisabethinen Hospital, Linz, Austria
[u] Federal University of Ceara, Fortaleza, Brazil
[v] Hanusch Hospital and Ludwig Boltzmann Cluster Oncology, Vienna, Austria
[w] Department of Internal Medicine I, Division of Hematology & Hemostaseology and Ludwig Boltzmann Cluster Oncology, Medical University of Vienna, Austria
[x] University Hospital of Innsbruck, Innsbruck, Austria
[y] University of Dundee, Dundee, United Kingdom
[z] Hospital Universitario Vall d'Hebron, Barcelona, Spain
[A] VU University Medical Center, Cancer Center Amsterdam, Amsterdam, The Netherlands
[B] Stanford Cancer Institute, Stanford, CA, United States

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ABSTRACT

Clinical features of myelodysplastic syndromes (MDS) could be influenced by many factors, such as disease intrinsic factors (e.g., morphologic, cytogenetic, molecular), extrinsic factors (e.g, management, environment), and ethnicity. Several previous studies have suggested such differences between Asian and European/USA countries. In this study, to elucidate potential differences in primary untreated MDS between Japanese (JPN) and Caucasians (CAUC), we analyzed the data from a large international database collected by the International

* Corresponding author at: Department of Hematology, Atomic Bomb Disease Institute, Nagasaki University, 1-12-4 Sakamoto, Nagasaki, 852-8523, Japan.
E-mail address: y-miyaza@nagasaki-u.ac.jp (Y. Miyazaki).

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Karyotype

Working Group for Prognosis of MDS (300 and 5838 patients, respectively). JPN MDS were significantly younger with more severe cytopenias, and cytogenetic differences: less del(5q) and more +1/+1q, -1/del(1p), der(1;7), -9/del(9q), del(16q), and del(20q). Although differences in time to acute myeloid leukemia transformation did not occur, a significantly better survival in JPN was demonstrated, even after the adjustment for age and FAB subtypes, especially in lower, but not in higher prognostic risk categories. Certain clinical factors (cytopenias, blast percentage, cytogenetic risk) had different impact on survival and time to transformation to leukemia between the two groups. Although possible confounding events (e.g., environment, diet, and access to care) could not be excluded, our results indicated the existence of clinically relevant ethnic differences regarding survival in MDS between JPN and CAUC patients. The good performance of the IPSS-R in both CAUC and JP patients underlines that its common risk model is adequate for CAUC and JP.

1. Introduction

Patients with myelodysplastic syndromes (MDS) show heterogeneous clinical features with variation in ineffective hematopoiesis, morphological dysplasia, and progression to acute myeloid leukemia (AML) [1]. MDS arises from abnormal hematopoietic stem cells, with detectable somatic mutations in virtually all patients [2,3], and recent studies also showed that germline mutations are found in a portion of MDS [4,5]. These results clearly demonstrate that the genomic status is highly influential on clinical features of MDS [3]. For example, *SF3B1* mutations and the presence of ring sideroblasts are strongly associated in MDS [6,7]. In some hematological neoplasms, incidences are related to ethnic differences. Chronic lymphocytic leukemia is more frequent in Caucasians (CAUC) than Japanese (JPN) [8,9] and could be attributable, at least in part, to susceptibility loci of the genome [10]. MDS appears to be more common in Non-Hispanic compared with Hispanic people [11]. These reports support the idea that genetic background affects the incidence of some hematological neoplasms, including MDS. Considering the importance of potential genetic differences in MDS, ethnic backgrounds could contribute not only to the differing incidence but also could affect the clinical courses of this group of disorders. Several reports from Asian countries suggested differences in clinical features of MDS in different parts of the world [12–15].

The treatment strategy for MDS is usually based on clinical features, patient-related factors, the biology of the MDS, and prognostic scoring systems including the International Prognostic Scoring System (IPSS) [16], and the revised IPSS (IPSS-R) [17]. The IPSS-R was developed using data from more than 7000 MDS patients, including CAUC and JPN. These two systems have been widely utilized and validated to predict overall survival (OS) and risk of AML transformation by many groups for ethnically different populations [18–23]. In this study, we analyzed this large International Working Group for Prognosis of MDS (IWG-PM) database, which generated the IPSS-R, to address the question of whether ethnic or other differences between JPN and CAUC MDS patients influenced their clinical features and outcomes. In contrast to previous reports, we compared clinical factors in more detail, with particular focus on cytogenetic abnormalities and clinical outcomes.

2. Patients and methods

2.1. Patients

The IWG-PM collected more than 7000 primary untreated MDS patients who had maintained clinical stability for at least 2 months, as in the original IPSS-R study [17], under the aegis of the MDS Foundation, Inc. We used both FAB [24] and WHO [25] classification in this study, because both were used in the original IPSS-R analysis. Patients were self-declared as White / Caucasian (CAUC) or Japanese (JPN). It is understood that the term Caucasian is inexact [26] but herein refers to those White non-Hispanic or Latino individuals of US or European derivation. CAUC patients came from US and EU centers; all JPN came from Japanese centers. There were 13 major centers (including more than 70 co-operating hospitals) contributed for CAUC patients' data, and 4 centers for JPN patients. In terms of JPN data, two data sets were from center hospitals (university academic hospitals), and other two were submitted from several hospitals (the number of hospitals were not clear after anonymization). We evaluated only patients whose ethnicity was indicated in the database (350 patients for JPN, and 6025 for CAUC), and then we further selected these cases by age. JPN MDS patients were significantly younger than CAUC patients, with median ages of 62 years (range 16–90) and 71 years (16–106), respectively ($P < 0.001$). Since patients of less than 40 years old comprised 14.3% of the JPN group compared to 3.1% of CAUC, to aid comparability, we restricted our analysis to patients older than 39 years in this study. Thus, the final number of JPN and CAUC patients for the analysis was 300 and 5838, respectively (6138 in total). For JPN, data were contributed by 4 sites (two from university hospitals, and two were collected from several hospitals); within the CAUC data came from 13 centers. The median year of diagnosis for these patients was 2001 (range 1964 to 2010). These sites obtained data in accordance with their respective institutional review board approvals.

2.2. Statistical methods

As a measure of prognostic power, the Dxy coefficient together with its 95% confidence interval for censored data [27] was used. Dxy is a concordance coefficient varying between -1 and 1, with 0 representing no predictive power and 1 perfect concordance of ascribed risk and survival and time to transformation, respectively. Adjusted curves for survival and time to AML were calculated by weighting the comparison subsample according to the distribution of the reference sample and tested by a related Cox model.

Depending on the concerned variables, p-values were taken from the Wilcoxon-Mann-Whitney-U-Test, Kendall's tau, the chi-square-test, or the logrank-Mantel-Cox-test. Two-sided P values less than 0.05 were considered significant. In line with the essentially exploratory nature of the project, no adjustment for multiple testing was applied. All analyses were performed using the open source software R version 3.2.3 [28] including the package "survival" [29].

3. Results

3.1. Background of the data selection

Table 1 shows the demographic details of the 40 years and over JPN and CAUC patient cohorts within the IWG-PM database analyzed in this study. In these cohorts, median age of JPN and CAUC patients was 65.5 and 71 years, and JPN patients were significantly younger (Table 1, $P < 0.001$). There was no difference in the distribution of gender.

3.2. FAB and WHO subtype

A significant difference in the distribution of FAB subgroups [24] (6136 cases) was noted between JPN and CAUC ($P < 0.001$, Table 1). In the JPN group, the frequency of the following FAB subtypes was

Table 1
Demographics of JPN and CAUC MDS in this study.

	JPN n (%)	CAUC n (%)	P value (U-Test)
Age	n = 300	n = 5838	< 0.001
median age	65.5	71	
Sex	n = 300	n = 5838	0.5391
male	180 (60)	3606 (61.77)	
female	120 (40)	2232 (38.23)	
ECOG PS	n = 59	n = 2192	0.0249
0	7 (11.86)	706 (32.21)	
1	48 (81.36)	1241 (56.61)	
2-4	4 (6.78)	245 (11.18)	
FAB classification	n = 300	n = 5836	< 0.001
RA	187 (62.3)	2280 (39.1)	
RARS	18 (6.0)	1082 (18.5)	
RAEB	66 (22.0)	1477 (25.3)	
RAEB-T	15 (5.0)	328 (5.6)	
CMML	14 (4.7)	590 (10.1)	
Others	0	79 (1.4)	
WHO classification	n = 226	n = 4460	< 0.001
RCUD	38 (16.8)	724 (16.2)	
RARS	9 (4.0)	560 (12.6)	
RCMD	93 (41.2)	1243 (27.9)	
RAEB-1	24 (10.6)	788 (17.7)	
RAEB-2	48 (21.2)	832 (18.7)	
5q-	3 (1.3)	210 (4.7)	
MDS-U	0	103 (2.3)	
Others	11(4.9)	0	
Hb	n = 300	n = 5836	< 0.001
median	85	99	
range	38-171	23-189	
PLT	n = 300	n = 5838	< 0.001
median	75	130	
range	1-1110	0-1540	
WBC	n = 253	n = 5580	< 0.001
median	3.1	4	
range	0.6-12.5	0.4-12.0	
ANC	n = 300	n = 5838	< 0.001
median	1.3	1.91	
range	0.12-8.0	0-10.6	
PB blast (%)	n = 178	n = 4105	0.003
median	0	0	
range	0-7	0-19	
blast < 1%	93.3	84.1	
BM blast (%)	n = 300	n = 5838	0.015
median	2	3	
range	0-28	0-30	
Serum ferritin	n = 138	n = 2502	< 0.001
median	216	342	
range	5-4370	0-10000	
Serum LD	n = 225	n = 3768	0.089
elevated over normal range	69 (30.7)	963 (25.6)	
RBC transion dependency	n = 177	n = 2498	0.038
No	132 (74.6)	1555 (67)	
Yes	45 (25.4)	766 (33)	
Cytogenetic risk category	n = 300	n = 5838	0.332
very good	3 (1)	210 (3.6)	
good	214 (71.3)	4216 (72.2)	
intermediate	51 (17)	774 (13.3)	
poor	13 (4.3)	238 (4.1)	
very poor	19 (6.3)	400 (6.9)	
Clinical risk category			
< IPSS-R >	n = 300	n = 5838	< 0.001
very low	30 (10)	1136 (19.5)	
low	95 (31.7)	2202 (37.7)	
int	96 (32)	1123 (19.2)	
high	40 (13.3)	766 (13.1)	
very high	39 (13)	611 (10.5)	
< IPSS >	n = 300	n = 5832	< 0.001
Low	60 (20)	2246 (38.5)	
Intermediate-1	177 (59)	2224 (38.1)	
Intermediate-2	40 (13.3)	954 (16.4)	
High	23 (7.7)	408 (7)	

ECOG PS, European clinical oncology group performance status; FAB, French-American-British;
RA, refractory anemia; RARS, RA with ring sideroblasts; RAEB, RA with excess blasts;
RAEB-T, RAEB in transformation; CMML, chronic myelomonocytic leukemia;
RCUD, refractory cytopenia with unilineage dysplasia; RCMD, RC with multilineage dysplasia;
5q-, 5q- syndrome; MDS-U, MDS unclassifiable; PB, peripheral blood; BM, bone marrow;
IPSS, international prognostic scoring system; IPSS-R, revised IPSS.

Table 2
Number and frequency of each karyotypic aberration.

	JPN	CAUC	
	number of cases (percentage)	number of cases (percentage)	P value
Karyotype	N = 261 (100)	N = 4844 (100)	
+1/+1q	5 (1.9)	35(0.7)	0.033
−1/del(1p)	6 (2.3)	27 (0.6)	< 0.001
der(1;7)	5 (1.9)	14 (0.3)	< 0.001
−9/del(9q)	6 (2.3)	31 (0.6)	0.002
del(16q)	4 (1.5)	10 (0.2)	< 0.001
del(20q)	18 (6.9)	135 (2.8)	< 0.001
-Y	3 (1.1)	164 (3.4)	0.048
del(5q)	5 (1.9)	415 (8.6)	< 0.001
inv(3)/t(3q)/del(3q)	2 (0.8)	17 (0.4)	0.283
t(5q)	0	16 (0.3)	0.353
t(7q)	0	10 (0.2)	0.463
−7	3 (1.1)	132 (2.7)	0.122
del(7q)	7 (2.7)	74 (1.5)	0.146
+8	10 (3.8)	280 (5.8)	0.185
+11	0	15 (0.3)	0.368
del(11q)	3 (1.1)	60 (1.2)	0.899
t(11q23)	0	7 (0.1)	0.539
del(12p)	3 (1.1)	61 (1.3)	0.877
+13	1 (0.4)	9 (0.2)	0.483
−13/del(13q)	2 (0.8)	40 (0.8)	0.918
del(17p)	3 (1.1)	28 (0.6)	0.247
i(17q)	2 (0.8)	14 (0.3)	0.179
+19	0	23 (0.5)	0.265
+21	0	42 (0.9)	0.131
−21/del(21q)	1 (0.4)	18 (0.4)	0.976
-X	0	16 (0.3)	0.353
marker chromosome	4 (1.5)	92 (1.9)	0.671

t(5q), some aberrations involving 5q; t(7q), some aberrations involving 7q.
t(11q23), translocations involving 11q23.

Table 3
Distribution of patients in age-adjusted IPSS-R category.

IPSS-RA[a] category	JPN n (%)	CAUC n (%)	P = 0.010
Very Low	38 (12.7)	1051 (18)	
Low	93 (31)	1959 (33.6)	
Intermediate	83 (27.7)	1313 (22.5)	
High	46 (15.3)	826 (14.1)	
Very High	40 (13.3)	689 (11.8)	
total	300 (100)	5838 (100)	

[a] IPSS-RA, age-adjusted IPSS-R.

lower than CAUC: refractory anemia with ring sideroblasts (RARS, 6.0% for JPN, and 18.5% for CAUC), and CMML (4.7% for JPN, and 10.1% for CAUC). In terms of WHO morphologic subtypes [25] (4686 cases), the distribution was also significantly different (P < 0.001, Table 1) with more refractory cytopenia with multilineage dysplasia (RCMD) in the JPN group (41.2% and 27.9% for JPN and CAUC, respectively), and less RARS (4.0% and 12.6%, for JPN and CAUC, respectively) and 5q- syndrome (1.3% and 4.7% for JPN and CAUC, respectively).

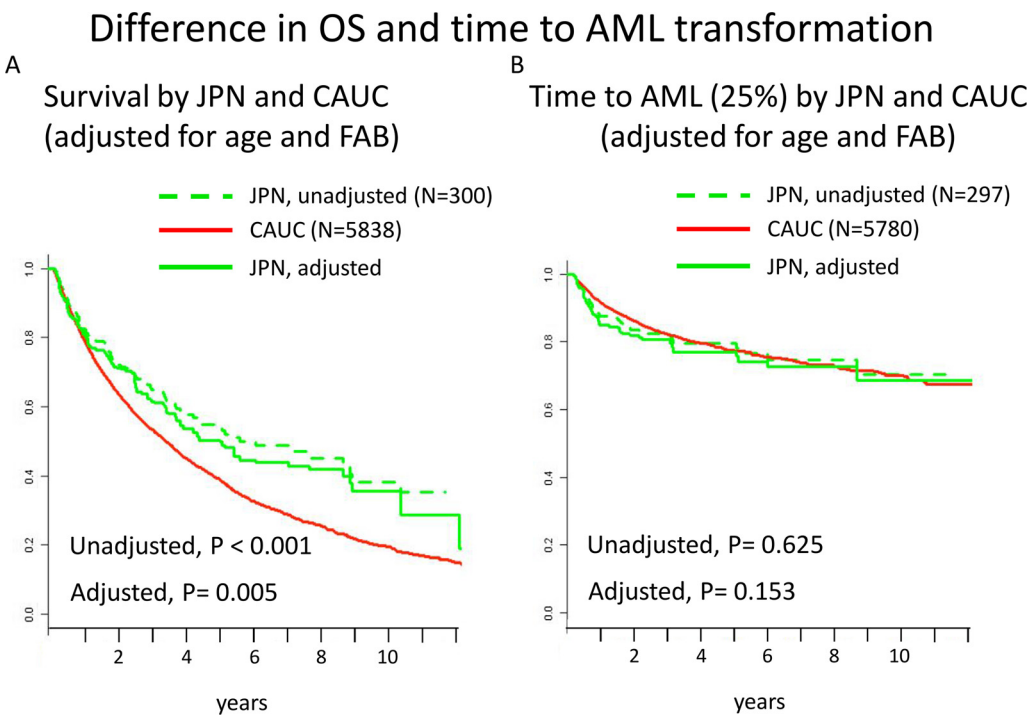

Fig. 1. Comparison of survival (A) and time to AML transformation (B) between JPN and CAUC MDS (Kaplan-Meier curves). Broken green lines represented survival curves of JPN with raw data. Green lines showed JPN data with the adjustment for age and FAB subtypes to those of CAUC. Red lines were for CAUC. There were significant differences in survival between two groups with or without adjustment, although the difference was smaller after the adjustment for age and FAB subtypes. There was no difference in time to AML transformation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.3. Hematological and laboratory data

Hematological and laboratory tests showed significantly lower values in white blood cells (WBC), absolute neutrophil count (ANC), hemoglobin (Hb), platelet (PLT), and ferritin in JPN than CAUC (Table 1). There was also significant difference in peripheral blood (PB) and bone marrow (BM) blast percentage between the two groups with less blasts in both PB and BM for JPN (P = 0.003, and P = 0.015, for PB and BM blast percentage, respectively).

3.4. Cytogenetic data and cytogenetic risk groups

The frequency of IPSS-R cytogenetic groups was compared between two groups [30]. The distribution in the cytogenetic risk groups (IPSS-R risk) was not different between JPN and CAUC (Table 1, P = 0.332). The percentage of normal karyotype was 65.3% and 62.7% in JPN (n = 300) and CAUC (n = 5838) groups, respectively, without significant difference (P = 0.382). To compare the frequency of each aberration used in IPSS-R risk stratification, data which met ISCN criteria were selected and further analyzed (n = 5105) [31]. Among 27 types of cytogenetic aberrations, we found significantly higher frequencies of +1/+1q, -1/del(1q), der(1;7), -9/del(9q), del(16q) and del (20q) in the JPN group (Table 2). Del(5q) was significantly lower among JPN (1.9%, 5 out of 261 cases) than CAUC patients (8.6%, 415 out of 4844 cases) (Table 2, P < 0.001). The differences in the cytogenetic abnormalities did not change in patients younger than 40 years (data not shown).

3.5. IPSS-R risk group and IPSS-RA score

For the comparison of IPSS-R between JPN and CAUC patients, initially raw IPSS-R scores were compared. The median IPSS-R score for JPN MDS was 3.5, which was significantly higher than that for CAUC (score = 3.0) (P < 0.001), and this difference was reflected in the distribution in IPSS-R risk groups (P < 0.001, Table 1). JPN group contained more Intermediate risk, and less Very Low risk patients. We next analyzed the score of age-adjusted IPSS-R (IPSS-RA).[18] The difference in IPSS-RA score between JPN (3.35) and CAUC (3.0) became smaller compared with IPSS-R raw scores, but the significant difference persisted (P = 0.007). When IPSS-RA was used to categorize MDS patients, significant difference remained in the distribution of patients between the two groups (P = 0.010, Table 3).

3.6. Overall survival and time to AML evolution

Statistically significant differences in the time to AML transformation between JPN and CAUC patients were not seen (P = 0.625, Fig. 1B). However, overall survival was significantly longer in JPN compared to CAUC patients (median survival time 67.5 and 41.5 months, respectively, P < 0.001, Fig. 1A). Because age and the distribution in FAB subtypes were markedly different between JPN and CAUC patients even in the groups aged 40 and older (Table 1), survival time and time to AML were re-calculated with the adjustment for these two factors. There was no significant difference in time to AML. However, survival was still longer in JPN patients (P = 0.005, Fig. 1A). Survival time after AML transformation was also different between two groups after adjustment for age and FAB: JPN and CAUC patients showed median survival time of 4.9 and 2.6 months, respectively (P = 0.009). This finding is consistent with the significant differences in overall survival between the two patient groups, given that JPN shows longer intervals before and after transformation. Survival difference remained when younger groups, for example, for patients under age 50 or 60 years, respectively, were considered (data not shown).

3.7. Impact of each factor in IPSS-R score on survival and time to AML, and application of IPSS-R for JPN MDS

To further analyze the differences in OS between JPN and CAUC, we compared OS by IPSS-R risk groups after adjustment for age and FAB subtypes. The survival difference between JPN and CAUC remained significant if simultaneously taking into account age, FAB and IPSS-R categories (P = 0.015). As shown in Table 4 and Fig. 2, OS of JPN and CAUC MDS were subdivided into five groups and demonstrated substantially increased OS of JPN patients in Very Low, Low, and Intermediate groups.

The impact of individual prognostic factors in the IPSS-R was

Table 4
Impact of factors on OS and time to AML transformation.

	OS of JPN			Time to AML transformatin of JPN				OS of CAUC			Time to AML transformation of CAUC		
	n (%)	med survival (yr)	Dxy (95%CI*) P value	n (%)	25% AML trans (yr)	Dxy (95%CI*) P value		n (%)	med survival (yr)	Dxy (95%CI*) P value	n (%)	25% AML trans (yr)	Dxy (95%CI*) P value
Cytogenetics	300 (100)		0.3 (0.19-0.41) P<0.001	297 (100)		0.08 (-0.08-0.24) P=0.014	Cytogenetics	5838 (100)		0.24 (0.22-0.26) P<0.001	5780 (100)		0.29 (0.25-0.33) P<0.001
very good	3 (1)	NR		3 (1.01)	NR		very good	210 (3.6)	5.1		207 (3.58)	NR	
good	214 (71.33)	8.9		211 (71.04)	8.7		good	4216 (72.22)	4.4		4171 (72.16)	9.4	
intermediate	51 (17)	4.4		51 (17.17)	NR		intermediate	774 (13.26)	2.4		766 (13.25)	2.3	
poor	13 (4.33)	1.9		13 (4.38)	3.1		poor	238 (4.08)	1.4		238 (4.12)	1.6	
very poor	19 (6.33)	0.6		19 (6.4)	0.3		very poor	400 (6.85)	0.6		398 (6.89)	0.7	
BM blast	300 (100)		0.44 (0.35-0.54) P<0.001	297 (100)		0.53 (0.38-0.68) P<0.001	BM blast	5838 (100)		0.29 (0.27-0.31) P<0.001	5780 (100)		0.47 (0.44-0.51) P<0.001
<=2	152 (50.67)	8.9		150 (50.51)	NR		<=2	2728 (46.73)	5.4		2699 (46.7)	15.6	
>2 to <5	61 (20.33)	5.6		60 (20.2)	NR		>2 to <5	1055 (18.07)	3.8		1039 (17.98)	7.6	
5 to 10	45 (15)	2.5		45 (15.15)	1.3		5 to 10	1139 (19.51)	2.1		1131 (19.57)	2.3	
>10	42 (14)	1.4		42 (14.14)	0.7		>10	916 (15.69)	1.3		911 (15.76)	0.9	
Hb	300 (100)		0.16 (0.05-0.27) P=0.001	297 (100)		0.09 (-0.06-0.25) P=0.384	Hb	5838 (100)		0.21 (0.19-0.23) P<0.001	5780 (100)		0.16 (0.12-0.2) P<0.001
>=100	94 (31.33)	12.5		93 (31.31)	6		>=100	2824 (48.37)	5.2		2802 (48.48)	9.5	
>=80 to <100	87 (29)	3.7		86 (28.96)	3.2		>=80 to <100	2108 (36.11)	2.6		2082 (36.02)	4.4	
<80	119 (39.67)	5		118 (39.73)	NR		<80	906 (15.52)	1.8		896 (15.5)	2.3	
PLT	300 (100)		0.01 (-0.12-0.12) P=0.651	297 (100)		0.06 (-0.09-0.21) P=0.275	PLT	5838 (100)		0.24 (0.22-0.26) P<0.001	5780 (100)		0.19 (0.15-0.22) P<0.001
>=100	119 (39.7)	6.1		119 (40.07)	6		>=100	3540 (60.64)	4.7		3496 (60.48)	8.5	
>=50 to <100	78 (26)	3.7		76 (25.59)	1.9		>=50 to <100	1228 (21.03)	2.6		1222 (21.14)	3.1	
<50	103 (34.3)	7.1		103 (34.34)	NR		<50	1070 (18.33)	1.4		1062 (18.37)	2.4	
ANC	300 (100)		0.06 (-0.03-0.16) P=0.120	297 (100)		0.15 (0-0.29) P=0.031	ANC	5838 (100)		0.11 (0.1-0.13) P<0.001	5780 (100)		0.17 (0.14-0.2) P<0.001
>=0.8	229 (76.33)	7.1		226 (76.09)	8.7		>=0.8	4824 (82.63)	4		4772 (82.56)	8.2	
<0.8	71 (23.67)	3.5		71 (23.91)	1.9		<0.8	1014 (17.37)	1.7		1008 (17.44)	1.7	
IPSS-R	300 (100)		0.51 (0.4-0.6) P<0.001	297 (100)		0.49 (0.35-0.63) P<0.001	IPSS-R	5838 (100)		0.42 (0.4-0.44) P<0.001	5780 (100)		0.53 (0.5-0.56) P<0.001
very low	30 (10)	NR		30 (10.1)	NR		very low	1136 (19.46)	8.1		1126 (19.48)	NR	
low	95 (31.67)	17.3		93 (31.31)	8.7		low	2202 (37.72)	4.8		2175 (37.63)	10.2	
int	96 (32)	5		95 (31.99)	NR		int	1123 (19.24)	2.7		1109 (19.19)	2.9	
high	40 (13.33)	2.1		40 (13.47)	0.7		high	766 (13.12)	1.5		761 (13.17)	1.4	
very high	39 (13)	0.9		39 (13.13)	0.9		very high	611 (10.47)	0.8		609 (10.54)	0.7	
Sex	300 (100)		0.06 (-0.04-0.16) P=0.393	297 (100)		0.07 (-0.08-0.21) P=0.304	Sex	5830 (100)		0.06 (0.04-0.08) P<0.001	5780 (100)		0.04 (0.00-0.07) P=0.043
Male	180 (60)	5.1		180 (60.61)	5.1		Male	3606 (61.77)	3		3573 (61.82)	5.8	
Female	120 (40)	7.1		117 (39.39)	8.7		Female	2232 (38.23)	4.2		2207 (38.18)	7.2	
Age	300 (100)		0.14 (0.05-0.23) P=0.001	297 (100)		0.13 (0.00-0.27) P=0.015	Age	5838 (100)		0.03 (0.01-0.05) P<0.001	5780 (100)		0.03 (0.00-0.06) P=0.284
<=60	108 (36)	17.3		105 (35.35)	NR		<=60	1078 (18.47)	4.7		1066 (18.44)	6.9	
>60	192 (64)	4.4		192 (64.65)	3.2		>60	4760 (81.53)	3.3		4714 (81.56)	6.3	
ECOG PS	59 (100)		0.07 (-0.13-0.27) P=0.274	56 (100)		-0.06 (-0.53-0.40) P=0.898	ECOG PS	2192 (100)		0.16 (0.13-0.19) P<0.001	2189 (100)		0.10 (0.04-0.16) P=0.006
0	7 (11.86)	8.9		6 (10.71)	5.1		0	706 (32.21)	4.1		704 (32.16)	NR	
1	48 (81.36)	7.7		46 (82.14)	NR		1	1241 (56.61)	2.1		1240 (56.65)	5.9	
2-4	4 (6.78)	2.9		4 (7.14)	0.6		2-4	245 (11.18)	1.7		245 (11.19)	2.8	
Serum ferritin	138 (100)		0.05 (-0.15-0.25) P=0.554	137 (100)		0.21 (-0.09-0.52) P=0.183	Serum ferritin	2502 (100)		0.14 (0.10-0.17) P<0.001	2497 (100)		0.09 (0.03-0.16) P=0.028
<=350	95 (68.84)	8.9		94 (68.61)	NR		<=350	1280 (51.16)	5.3		1278 (51.18)	10.2	
>350	43 (31.16)	7.7		43 (31.39)	5.1		>350	1222 (48.84)	3.6		1219 (48.82)	14.5	
Serum LD	225 (100)		0.06 (-0.06-0.19) P=0.557	222 (100)		0.06 (-0.10-0.21) P=0.611	Serum LD	3768 (100)		0.12 (0.10-0.14) P<0.001	3761 (100)		0.14 (0.10-0.19) P<0.001
Normal	156 (69.33)	8.7		153 (68.92)	6		Normal	2805 (74.44)	3.8		2800 (74.45)	9.5	
High	69 (30.67)	7.1		69 (31.08)	NR		High	963 (25.56)	2		961 (25.55)	2.9	
RBC trans dep	177 (100)		0.14 (-0.02-0.30) P=0.009	174 (100)		0.03 (-0.17-0.23) P=0.527	RBC trans dep	2321 (100)		0.24 (0.21-0.27) P<0.001	2317 (100)		0.27 (0.22-0.32) P<0.001
No	132 (74.58)	NR		129 (74.14)	8.7		No	1555 (67)	5.9		1552 (66.98)	10.2	
Yes	45 (25.42)	7.1		45 (25.86)	6		Yes	766 (33)	2		765 (33.02)	2	
IPSS	300 (100)		0.45 (0.36-0.54) P<0.001	277 (100)		0.45 (0.36-0.54) P<0.001	IPSS	5832 (100)		0.36 (0.34-0.38) P<0.001	5774 (100)		0.49 (0.46-0.52) P<0.001
Low	60 (20)	17.3		60 (20)	NR		Low	2246 (38.51)	6.3		2215 (38.36)	14.5	
Intermediate-1	177 (59)	8.7		174 (58.59)	8.7		Intermediate-1	2224 (38.13)	3.2		2206 (38.21)	5.5	
Intermediate-2	40 (13.33)	1.2		40 (13.47)	0		Intermediate-2	954 (16.36)	1.4		947 (16.4)	1.2	
High	23 (7.67)	0.7		23 (7.74)	0.7		High	408 (7)	0.9		406 (7.03)	0.7	

* 95% confidence interval

25% AML trans, time to transform AML in 25% of the patients

NR, not reached

* 95% confidence interval.
25% AML trans, time to transform AML in 25% of the patients.
NR, not reached.

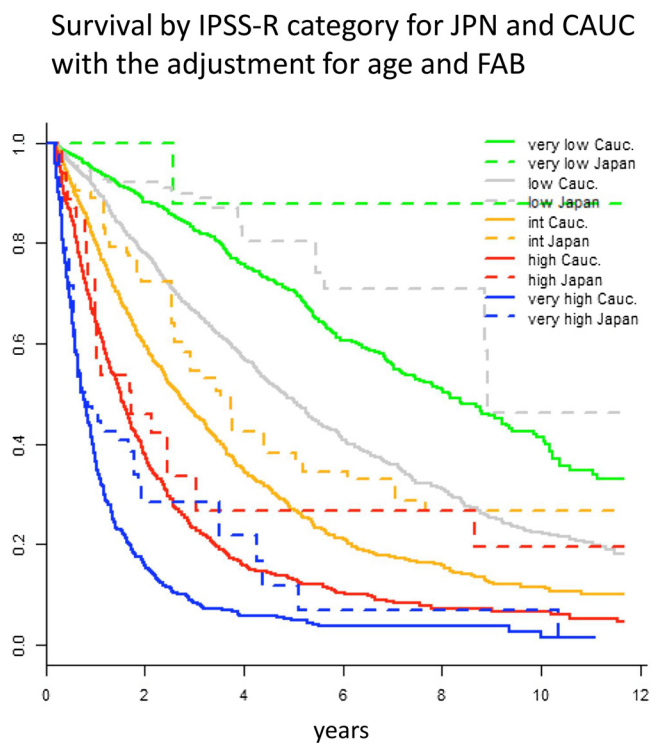

Fig. 2. Comparison of survival between JPN and CAUC MDS by IPSS-R risk categories (Kaplan-Meier curves) with the adjustment for age and FAB subtypes. (For interpretation of the references to colour in this figure, the reader is referred to the web version of this article.)

evaluated (Table 4). In the comparison between JPN and CAUC, Dxy values for cytopenias (i.e., levels of Hb, PTL, and ANC) were smaller in JPN than CAUC, demonstrating smaller prognostic impact on survival and time to AML transformation. Some P values for Dxy of cytopenia-related factors showed no significant impact among JPN patients. On the other hand, Dxy of BM blast percentage was larger in JPN for both OS and time to AML transformation than CAUC. Dxy of cytogenetic risk group for JPN was larger for OS, but smaller for time to AML than CAUC. IPSS-R that combined these factors in JPN showed 0.51 for OS and 0.49 for time to AML, which were comparable to those of CAUC (0.42 and 0.53 for OS and time to AML, respectively). These data indicated a stronger impact of blast percentage and cytogenetics as compared to cytopenias on outcomes in the IPSS-R for JPN vs CAUC.

4. Discussion

In this study, by comparing clinical features of JPN and CAUC MDS patients, we found a striking difference in OS, but not in time to AML transformation. The improved survival difference between JPN and CAUC remained significant even when simultaneously taking into account age, FAB and IPSS-R categories. The difference in OS was large, especially in lower-risk IPSS-R categories Very Low, Low, and Intermediate risk groups. Several clinical factors were also found significantly different between the two patient groups. These factors were age, levels of cytopenias, percentages of PB and BM blasts, serum ferritin, and the frequencies of several karyotypes. Among them, the median values of ANC and ferritin in JPN centers were smaller than those of each CAUC center, respectively. Except for one JPN center, the same was true for hemoglobin and platelets. These findings indicated the presence of markedly, significant difference in these factors between JPN and CAUC. Although there was no significant difference in the frequency of dysplasia in three lineages (data not shown), the distributions in FAB and WHO morphologic subtypes also showed differences. The differences in classifications were mainly found in those with low blast percentages (RA and RARS in FAB, and RARS, RCMD and 5q-syndrome in WHO classifications). Significantly lower PB and BM blast percentages in JPN was reflected, at least in part, in the different percentage of RAEB-1 in WHO classification (10.6% for JPN, and 17.7% for CAUC), though those of RAEB-2 were similar (21.2% for JPN, and 18.7% for CAUC).

In our relatively large JPN patient cohort, new differential features were identified between JPN and CAUC, including differing karyotypic frequencies and differences in OS. The incidence of +1/+1q, -1/del (1q), der(1;7), -9/del(9q), del(16q) and del(20q) was significantly increased in JPN while Del(5q) was decreased.

The difference in OS between JPN and CAUC was still observed after the adjustment for age and FAB subtypes in the two groups, demonstrating that younger age of JPN patients was not crucial for the significant difference in OS. IPSS-R score (and IPSS-RA score) was higher in JPN, but OS was longer in JPN. This suggested that the clinical factors used in IPSS-R had different impact on OS in JPN and CAUC. The analysis demonstrated that Dxy's of cytopenias was smaller, and those for BM blasts and cytogenetic risk category were higher for OS but not for AML transformation in JPN than CAUC patients. These findings fit the results of OS and AML comparisons in these two patient cohorts. Importantly, these patients were all untreated by disease-modifying agents. Thus, the influence of such treatments on OS would not have confounded the results. Several explanations exist regarding possible reasons for the demonstrated survival differences between JPN and CAUC: differences in disease subgroup distribution, patients' care, environmental factors including diet, incidence of accompanying diseases such as cardiovascular diseases or other malignancies, and clinically relevant ethnic features. The survival differences between JP and CAUC, particularly in lower risk categories are concordant with a comparatively low general mortality in Japan [32].

Some of these differences were previously found in studies comparing MDS of an Asian country and European countries with or without USA [12–15]. In the report comparing JPN and German RA [15], the authors showed that JPN patients were younger, and had more severe cytopenias, less del(5q), and better OS. In our study, we compared individual MDS subtypes with larger numbers of JPN and a broader group of CAUC patients, and confirmed and extended the previous findings. Other reports from China [12], Thailand [13], and Korea [14] also reported younger ages of MDS patients, suggesting that this is a common characteristic of Asian MDS. Recently, a Japanese group reported clinical features of a group of MDS patients (not included in this study) with data from 2006 to 2016, and demonstrated a median age of 68 years [22], which was older than the age of JPN in our cohort, albeit still younger than that of CAUC. This may relate to the rapid aging of recent Japanese society.

In summary, our results indicated that clinically relevant hematological, cytogenetic, and survival differences existed between JPN and CAUC MDS, and that the IPSS-R differentiates risk groups in JPN as well as CAUC patients. Detailed genome sequence and mutational analysis comparison between JPN and CAUC MDS will likely provide further useful answers to issues underlying such differences between these patient cohorts. Although it is in principle impossible to be sure about the causes of the differences, such investigations may stimulate clinically promising hypotheses. The potential existence of ethnic differences could raise concerns about the adequacy of combined analyses, but the good performance of the IPSS-R in both CAUC and JP patients underlines that this can successfully be done, as long as ethnically heterogeneous data is analyzed properly i.e. by stratification, as it was done in the development of the IPSS-R.

Disclosure

The authors declare no competing financial interests.

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